

*AMENDMENTS TO THE CLAIMS*

This listing of claims replaces all prior versions, and listings, of claims in the application.

1.-27. (Canceled)

28. (Currently Amended) A computer-readable recording medium containing a program for designing a physiologically active peptide capable of interacting with a target protein, allowing a computer to execute:

(a3) a step for exhaustively generating amino acid sequences of constant length, and randomly selecting amino acid sequences from among them for extraction as a library for analysis,

(b3) a step for calculating an intermolecular energy parameter ~~for~~ between each of the amino acid sequences extracted as a library for analysis and a target site of the target protein,

(c3) a step for generating a score matrix based on amino acid prevalence using ~~an~~ the intermolecular energy parameter calculated in step (b3),

(d3) a step for calculating a score based on amino acid prevalence using ~~[[a]]~~ the score matrix based on amino acid prevalence generated in step (c3),

(e3) a step for conducting a correlation analysis between ~~an~~ the intermolecular energy parameter calculated in step (b3) and said score to obtain a regression equation,

(f3) a step for converting ~~[[a]]~~ the score matrix based on amino acid prevalence generated in step (c3) to a matrix based on an amino acid position-dependent intermolecular energy parameter using said regression equation,

(g3) a step for calculating an amino acid position-dependent intermolecular energy parameter value from ~~[[a]]~~ the matrix based on an amino acid position-dependent intermolecular energy parameter converted in step (f3),

(h3) a step for extracting ~~an~~ amino acid ~~sequence~~ sequences not higher than a specified amino acid position-dependent intermolecular energy parameter value,

(i3) a step for calculating an intermolecular energy parameter with ~~[[a]]~~ the target site of the target protein, for the ~~extracted~~ amino acid ~~sequence~~ sequences extracted in step (h3),

(j3) a step for storing ~~said~~ the amino acid ~~sequence~~ sequences extracted in step (h3), along with ~~said~~ the intermolecular energy parameter calculated in step (i3), in a storage,

(k3) a step for extracting a specified number of amino acid sequences on the basis of information stored by step (j3), and

(l3) a step for displaying ~~an~~ the amino acid ~~sequence~~ sequences extracted in step (k3) as ~~a candidate~~ candidates for a physiologically active peptide.

29. (Canceled)

30. (Currently Amended) The computer-readable recording medium of claim 28, wherein the program further allows a computer to execute between step (k3) and step (l3):

(I) a step for generating ~~an~~ amino acid ~~sequence~~ sequences with an amino acid variation introduced to ~~an~~ the amino acid ~~sequence~~ sequences extracted in step (k3),

(II) a step for calculating an intermolecular energy parameter between ~~an~~ the amino acid ~~sequence~~ sequences generated in step (I) and ~~[[a]]~~ the target site of the target protein, and

(III) a step for comparing ~~an~~ the intermolecular energy parameter calculated in step (II) with an intermolecular energy parameter between ~~an~~ the amino acid ~~sequence~~ sequences extracted in step (k3) and ~~[[a]]~~ the target site of the target protein as a control, and extracting ~~an~~ amino acid ~~sequence~~ sequences having an intermolecular energy parameter that ~~is~~ are more stable than the intermolecular energy parameter of the control.

31. (Canceled)

32. (Currently Amended) An apparatus for designing a physiologically active peptide capable of interacting with a target protein, provided with (A3) a first amino acid sequence search portion, (B3) a first intermolecular energy calculation portion, (C3) a score matrix generation portion, (D3) a score calculation portion, (E3) a regression equation

generation portion, (F3) a matrix conversion portion, (G3) an amino acid position-dependent energy calculation portion, (H3) a second amino acid sequence search portion, (I3) a second intermolecular energy calculation portion, (J3) an amino acid sequence memory portion, (K3) a third amino acid sequence search portion, and (L3) an amino acid sequence display portion, wherein:

said first amino acid sequence search portion includes (a3) a means of exhaustively generating amino acid sequences of constant length, and randomly selecting amino acid sequences from among them for extraction as a library for analysis,

said first intermolecular energy calculation portion includes (b3) a means of calculating an intermolecular energy parameter ~~for~~ between each of the amino acid sequences extracted as a library for analysis and a target site of the target antigen,

said score matrix generation portion includes (c3) a means of generating a score matrix based on amino acid prevalence using ~~an~~ the intermolecular energy parameter calculated by means ~~(b3)~~ (b3),

said score calculation portion includes (d3) a means of calculating a score based on amino acid prevalence using ~~[[a]]~~ the score matrix based on amino acid prevalence generated by means (c3),

said regression equation generation portion includes (e3) a means of conducting a correlation analysis between ~~an~~ the intermolecular energy parameter calculated by means ~~(b3)~~ (b3) and said score to obtain a regression equation,

said matrix conversion portion includes (f3) a means of converting ~~[[a]]~~ the score matrix based on amino acid prevalence generated by means (c3) to a matrix based on an amino acid position-dependent intermolecular energy parameter using said regression equation,

said amino acid position-dependent energy calculation portion includes (g3) a means of calculating an amino acid position-dependent intermolecular energy parameter value from ~~[[a]]~~ the matrix based on an amino acid position-dependent intermolecular energy parameter converted by means (f3),

said second amino acid sequence search portion includes (h3) a means of extracting ~~an amino acid sequence~~ sequences not higher than a specified amino acid position-dependent intermolecular energy parameter value,

said second intermolecular energy calculation portion includes (i) a means of calculating an intermolecular energy parameter with ~~[[a]]~~ the target site of the target protein, for ~~an extracted the amino acid sequence~~ sequences extracted by means (h3),

said amino acid sequence memory portion includes (ii) a means of storing ~~said the~~ amino acid ~~sequence~~, sequences extracted by means (h3), along with ~~said the~~ intermolecular energy ~~parameter~~, parameter calculated by means (i), in a storage,

said third amino acid sequence search portion includes (iii) a means of extracting a specified number of amino acid sequences on the basis of information stored by ~~step means~~ (ii), and

said amino acid sequence display portion includes (iv) a means of displaying ~~an the~~ amino acid ~~sequence~~ sequences extracted in step by means (iii) as ~~a candidate~~ candidates for a physiologically active peptide.

33. (Canceled)

34. (Currently Amended) A method of designing a physiologically active peptide capable of interacting with a target protein, which method comprises ~~comprising allowing a computer to execute:~~

(a3) a step for exhaustively generating amino acid sequences of constant length, and randomly selecting amino acid sequences from among them for extraction as a library for analysis, wherein step (a3) is executed by computer,

(b3) a step for calculating an intermolecular energy parameter ~~for~~ between each of the amino acid sequences extracted as a library for analysis and a target site of the target protein, wherein step (b3) is executed by a computer,

(c3) a step for generating a score matrix based on amino acid prevalence using ~~an~~ the intermolecular energy parameter calculated in step (b3), wherein step (c3) is executed by computer,

(d3) a step for calculating a score based on amino acid prevalence using [[a]] the score matrix based on amino acid prevalence generated in step (c3), wherein step (d3) is executed by a computer,

(e3) a step for conducting a correlation analysis between ~~an~~ the intermolecular energy parameter calculated in step (b3) and said score to obtain a regression equation, wherein step (e3) is executed by a computer,

(f3) a step for converting [[a]] the score matrix based on amino acid prevalence generated in step (c3) to a matrix based on an amino acid position-dependent intermolecular energy parameter using said regression equation, wherein step (f3) is executed by a computer,

(g3) a step for calculating an amino acid position-dependent intermolecular energy parameter value from [[a]] the matrix based on an amino acid position-dependent intermolecular energy parameter converted in step (c3), wherein step (g3) is executed by a computer,

(h3) a step for extracting ~~an~~ amino acid ~~sequence~~ sequences not higher than a specified amino acid position-dependent intermolecular energy parameter value, wherein step (h3) is executed by a computer,

(i3) a step for calculating an intermolecular energy parameter with [[a]] the target site of the target protein, for the extracted amino acid ~~sequence~~ sequences extracted in step (h3), wherein step (i3) is executed by a computer,

(j3) a step for storing ~~said~~ the amino acid ~~sequence~~ sequences extracted in step (h3), along with said the intermolecular energy parameter calculated in step (i3), wherein step (j3) is executed by a computer,

(k3) a step for extracting a specified number of complementary amino acid sequences on the basis of information stored by step (j3), wherein step (k3) is executed by a computer, and

(I) a step for generating amino acid sequences with an amino acid variation introduced to the amino acid sequences extracted in step (k3), wherein step (I) is executed by a computer,

(II) a step for calculating an intermolecular energy parameter between the amino acid sequences generated in step (I) and the target site of the target protein, wherein step (II) is executed by a computer, and

(III) a step for comparing the intermolecular energy parameter calculated in step (II) with an intermolecular energy parameter between an amino acid sequence extracted in step (k3) and a target site of the target protein as a control, and extracting amino acid sequences having an intermolecular energy parameter that are more stable than the intermolecular energy parameter of the control, wherein step (III) is executed by a computer, and

(13) a step for displaying ~~an~~ the amino acid ~~sequence~~ ~~sequences~~ extracted by step (III) ~~(k3)~~ as ~~a candidate~~ candidates for a physiologically active peptide, wherein step (13) is executed by a computer.

35. (Currently Amended) The method of claim 34, which further comprises extracting, by method 1, complementary amino acid sequences for a target amino acid sequence of the target protein and/or extracting, by method 2, ~~an~~ amino acid ~~sequence~~ sequences of an optionally chosen length from the interaction region for the target protein, wherein the method 1 comprises:

(a1) a step for accepting an entry of sequence data on ~~[[a]]~~ the target amino acid sequence, wherein step (a1) is executed by a computer,

(b1) a step for converting ~~said~~ the target amino acid sequence to one or more moving average profile waveforms in accordance with one or more specified amino acid indices, wherein step (b1) is executed by a computer,

(c1) a step for generating ~~a candidate~~ candidates for an amino acid sequence complementary to the target amino acid sequence, and converting ~~it~~ them to one or more

complementary moving average profile waveforms using the same one or more amino acid indices as those in step (b1), wherein step (c1) is executed by a computer,

(d1) a step for calculating each of complementariness parameters from the same amino acid index between one or more moving average profile waveforms for ~~said target~~ the target amino acid sequence and one or more complementary moving average profile waveforms of ~~a candidate~~ the candidates for a complementary amino acid sequence generated in step (c1), wherein step (d1) is executed by a computer,

(e1) a step for storing ~~a candidate~~ the candidates for a complementary amino acid sequence, sequence generated in step (c1), along with said complementariness parameter parameters, in a storage, wherein step (e1) is executed by a computer, and

(f1) a step for extracting a specified number of complementary amino acid sequences on the basis of information stored by step (e1), wherein step (f1) is executed by a computer, and the method 2 comprises:

(a2) a step for identifying the interaction region in a protein that interacts with ~~[[a]]~~ the target site of the target protein, wherein step (a2) is executed by a computer, and

(b2) a step for extracting ~~an amino acid sequence~~ sequences of an optionally chosen length from ~~said the~~ the interaction region, wherein step (b2) is executed by a computer.

36. (Currently Amended) The method of claim 35, wherein said complementariness parameter is the correlation coefficient between a moving average profile waveform for said target amino acid sequence and a complementary moving average profile waveform of a candidate for a complementary amino acid sequence.

37. (Previously Presented) The method of claim 35, wherein said amino acid index is one or more indices selected from among indices based on the degree of hydrophobicity, indices based on an electric property, indices showing the likelihood of taking the  $\alpha$ -helix and  $\beta$ -sheet, and indices showing the relative size of side chain volume.

38. (Currently Amended) The method of claim 35, wherein the specified number of complementary amino acid sequences extracted in steps (a1) - (f1) using one or more specified amino acid indices ~~characterized in that the number of candidates for~~

~~complementary amino acid sequence extracted as physiologically active peptides~~ is narrowed down by taking steps (b1) - (f1), ~~(b1) - (f1) for a specified number of complementary amino acid sequences extracted in steps (a1) - (f1) using one or more specified amino acid indices, in one or more repeats, using one or more other amino acid indices.~~

39.-40. (Canceled)

41. (Currently Amended) The computer-readable recording medium of claim 28, wherein the program further allows a computer to execute the following steps (a1) - (f1):

(a1) a step for accepting an entry of sequence data on a target amino acid sequence of the target protein,

(b1) a step for converting said target amino acid sequence to one or more moving average profile waveforms in accordance with one or more specified amino acid indices,

(c1) a step for generating ~~a candidate~~ candidates for an amino acid sequence complementary to the target amino acid sequence of step (a1), and converting ~~it~~ them to one or more complementary moving average profile waveforms using the same one or more amino acid indices as those in step (b1),

(d1) a step for calculating each of complementariness parameters from the same amino acid index between one or more moving average profile waveforms for said target amino acid sequence and one or more complementary moving average profile waveforms of ~~a candidate~~ the candidates for a complementary amino acid sequence generated in step (c1),

(e1) a step for storing ~~a candidate~~ the candidates for a complementary amino acid sequence generated in step (c1), along with said complementariness parameter, and

(f1) a step for extracting a specified number of complementary amino acid sequences on the basis of information stored by step (e1), and/or the following steps (a2) - (b2):

(a2) a step for identifying the interaction region in a protein that interacts with [[a]] the target site of the target protein, and



(b2) a step for extracting ~~an~~ amino acid ~~sequence~~ sequences of an optionally chosen length from said interaction region.

42. (Currently Amended) The computer-readable recording medium of claim 41, wherein said complementariness parameter is the correlation coefficient between a moving average profile waveform for said target amino acid sequence and a complementary moving average profile waveform of a candidate for a complementary amino acid sequence.

43. (Previously Presented) The computer-readable recording medium of claim 41, wherein said amino acid index is one or more indices selected from among indices based on the degree of hydrophobicity, indices based on an electric property, indices showing the likelihood of taking the  $\alpha$ -helix and  $\beta$ -sheet, and indices showing the relative size of side chain volume.

44. (Currently Amended) The computer-readable recording medium of claim 41, wherein the specified number of complementary amino acid sequences extracted in steps (a1) - (f1) using one or more specified amino acid indices ~~characterized in that the number of candidates for complementary amino acid sequence extracted as physiologically active peptides is narrowed down by taking steps (b1) - (f1), (b1) - (f1) for a specified number of complementary amino acid sequences extracted in steps (a1) - (f1) using one or more specified amino acid indices,~~ in one or more repeats, using one or more other amino acid indices.

45. (Canceled)

46. (Currently Amended) The apparatus of claim 32, for processing the amino acid sequences extracted by step (f1) and/or (b2) in the second intermolecular energy calculation portion, the amino acid sequence memory portion, the third amino acid sequence search portion, and the amino acid sequence display portion, further provided with the following constitution 1:

(A) a data entry portion, (B) a data editing portion, (C) a complementary amino acid sequence candidate generation portion, (D) a complementariness calculation portion, portion, (E) a complementary amino acid sequence candidate memory portion, and (F) a complementary amino acid sequence search portion,

and/or the following constitution 2:

(A2) an interaction region identification portion, and (B2) a first interaction region amino acid sequence search portion,

wherein, in said constitution 1:

said data entry portion includes (a1) a means of accepting an entry of sequence data on a target amino acid sequence,

said data editing portion includes (b1) a means of converting said target amino acid sequence to one or more moving average profile waveforms in accordance with one or more specified amino acid indices,

said complementary amino acid sequence candidate generation portion includes (c1) a means of generating ~~a candidate~~ candidates for an amino acid sequence complementary to the target amino acid sequence of means (a1), and converting ~~it~~ them to one or more complementary moving average profile waveforms using the same one or more amino acid indices as those for means (b1),

said complementariness calculation portion includes (d1) a means of calculating each of complementariness parameters from the same amino acid index between one or more moving average profile waveforms for ~~said the~~ target amino acid sequence of means (a1) and one or more complementary moving average profile waveforms of ~~a candidate~~ the candidates for complementary amino acid sequence generated by means (c1),

said complementary amino acid sequence candidate memory portion includes (e1) a means of storing ~~a candidate~~ the candidates for a complementary amino acid sequence generated by means (c1), along with said complementariness ~~parameter~~ parameters, and

said complementary amino acid sequence search portion includes (f1) a means of extracting a specified number of complementary amino acid sequences on the basis of information stored by means (e1), and

wherein, in said constitution 2:

said interaction region identification portion in said constitution 2 includes (a2) a means of identifying the interaction region in a protein molecule that interacts with ~~[[a]]~~ the target site of the target protein, and

said first amino acid sequence search portion includes (b2) a means of extracting ~~an~~ amino acid ~~sequence~~ sequences of an optionally chosen length from said interaction region.

47. (Previously Presented) The computer-readable recording medium of claim 28, wherein the medium is selected from the group consisting of a magnetic tape, magnetic disc, magnetic drum, integrated circuit (IC) card, and optical disc.